Researchers identify new target for creating flavivirus vaccines

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Deepta Bhattacharya, PhD, works in his laboratory at the University of Arizona Health Sciences. Credit: University of Arizona Health Sciences, Noelle Haro-Gomez

The results of a recent study moved University of Arizona Health

Sciences researchers one step closer to developing effective vaccinations against flaviviruses, which infect more than 400 million people a year with diseases such as dengue, yellow fever, West Nile, Zika and Japanese encephalitis.

When a person is infected with a virus, antibodies are produced to fight the virus and provide immunity against reinfection. In the case of flaviviruses, however, if a person gets a second flavivirus infection —they were originally infected with Zika and then got dengue, for instance—the presence of antibodies can result in more severe symptoms through a process called antibody-dependent enhancement of infection.

"If, at some point in the past you've had Zika virus, later when you are exposed to dengue, you are at much greater risk of getting sick. Antibodies created by memory B cells as a result of the Zika infection can bind to certain parts of the dengue virus, but the dengue virus isn't affected," said Deepta Bhattacharya, Ph.D., an associate professor in the UArizona College of Medicine—Tucson's Department of Immunobiology. "In fact, the memory B cell-generated antibodies can work like a 'Trojan horse' and help the virus get into the cells, where it can make the disease worse."

The findings give Dr. Bhattacharya and his team a new way to think about creating flavivirus vaccines. Rather than targeting the whole virus, they propose targeting specific locations on the virus that are unique to each type and strain. Essentially, they would be removing memory B cells from the vaccination equation.

"We wanted to study how the immune system and antibody responses deal with sequential exposures to different flaviviruses," Dr. Bhattacharya said. "Antibody-dependent enhancement of infection is the main reason why it has been difficult to vaccinate against flaviviruses,

dengue in particular."

Dr. Bhattacharya is the senior author on a paper, "Affinity-restricted memory B cells dominate recall responses to heterologous flavivirus challenges," published today in the journal *Immunity*. The study focused on two types of cells that produce antibodies: plasma cells and memory B cells.

Plasma cells are the primary drivers of long-lasting immunity, as they continue to produce antibodies once an infection has been cleared or after vaccination. Memory B cells only produce antibodies if a second infection occurs.

"One of the questions we've had for a long time is, what is the purpose of those memory B cells?" said Dr. Bhattacharya, also a member of the university's BIO5 Institute. "If you already have antibodies from plasma cells, why do you need the other cells?"

Using a combination of flavivirus infections, vaccinations and genetic mouse models, Dr. Bhattacharya and his team examined how memory B cells respond to subsequent flavivirus infections.

They found that when memory B cells are activated by a new infection, they produce antibodies that are diverse and capable of targeting viruses that have changed since the first infection, through mutation or infection with a slightly different strain, for example.

"There is a huge amount of hidden diversity in memory B cells. For most viral pathogens, like influenza or SARS-CoV-2, this is a good thing. It means that memory B cells are poised to make new antibodies and deal with mutations if and when they arise," Dr. Bhattacharya said. "For flaviviruses, this is not so great. We found that memory B cells produce a lot of suboptimal antibodies that could enhance the second infection."

Although memory B cells recognize the new virus as a flavivirus and produce antibodies, those antibodies are unable to stop the new virus from infecting cells. In fact, they may actually make the second infection worse.

The same holds true when it comes to vaccinations. Vaccines are designed to stimulate an immune response and prompt plasma cells and memory B cells to produce antibodies against a virus. If a person who never had dengue is vaccinated and develops antibodies, then later becomes infected with a different flavivirus, the antibodies produced by memory B cells in response to the vaccination may increase the severity of the disease.

"For people already immune to one flavivirus, this would avoid engaging these not-so-great memory B cells," Dr. Bhattacharya said. "For people who never were exposed, it avoids generating this problematic diversity in the first place."

More information: Rachel Wong et al, Affinity-Restricted Memory B Cells Dominate Recall Responses to Heterologous Flaviviruses, *Immunity* (2020). DOI: 10.1016/j.immuni.2020.09.001

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